

REMARKS

Claims 1 to 4, 6 to 32, 34, 35 and 41 are under consideration. By this response, claims 3 to 12 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit or priority of the subject application. Accordingly, upon entry of this Response, claims 1, 2, 13 to 35 and 41 are under consideration.

Regarding the Amendments

The amendments are supported throughout the specification. In particular, the amendment to recite “Factor VII or Factor IX” is supported, for example, by claim 4 as originally filed. The amendment to recite a proteolytic cleavage site “having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1)” is supported, for example, by claim 9 as originally filed. Thus, as the amendments are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Claim Objection

Claim stands objected to due to absence of a SEQ ID NO for Arg Lys Arg. Claim 9 has been cancelled herein without prejudice. Accordingly the objection to claim 9 is moot.

I. **REJECTION UNDER 35 U.S.C. §112**

The rejection of claims 1 to 4, 6 to 8, 10, 13 to 32, 34, 35 and 41 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. Allegedly, these claims contain subject matter not described in the specification such that the skilled artisan would be reasonably apprised that Applicants had possession of the claimed invention, namely allegedly “the specification does not disclose a sufficient number of proteolytic cleavage sites to sufficiently represent the genus of polynucleotides.”

Claims 1 to 4, 6 to 8, 10, 13 to 32, 34, 35 and 41 are adequately described under 35 U.S.C. §112, first paragraph. Nevertheless, solely in order to expedite prosecution and without acquiescing to the propriety of the rejection, claims 3 to 12 have been cancelled herein without prejudice and the remaining claims have been amended as set forth above. The rejection of

claims 3 to 12 is therefore moot and will be addressed as if applied to the claims under consideration upon entry of the amendments.

Claim 1 has been amended to recite a proteolytic cleavage site “having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1).” The proteolytic cleavage site is defined structurally, such that the skilled artisan would be apprised of the proteolytic cleavage site. Consequently, an adequate written description is provided for the proteolytic cleavage site. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §102 and 103(a)

The rejection of claims 1 to 4, 6 to 12, 15, 1, 21 to 27, 29 to 32, 34, 35 and 41 under 35 U.S.C. §102(b), as allegedly anticipated by WO 98/38317 (Himmelsbach), as represented by U.S. Patent No. 6,573,071 (hereinafter the ‘071 patent) is respectfully traversed. Allegedly, WO 98/38317 (the ‘071 patent) describes each and every element of the rejected claims, for reasons set forth in the Office Action, pages 6-7.

Applicants first respectfully traverse the assertions in the Office Action that certain language of claims 1, 15 and 35 allegedly lacking patentable weight under 102(b) (page 6). In this regard, the assertions are either overly broad or inaccurate. Solely for the purpose of compact prosecution and without conceding that any of the assertions have merit, Applicants provide a brief traversal.

In claim 1, not all proteolytic cleavage sites can be cleaved when expressed in an animal cell. As an example, Applicants respectfully direct the Examiner’s attention to the cited ‘071 patent. Introduction of a furin cleavage site into FX and expression of this FX analogue in CHO cells did not result in protein bands corresponding to the activated forms of the protein (35 kD and 31 kD). This data led Himmelsbach to conclude that “the structure of the cleavage site region or the neighboring amino acid sequence seem to represent a suboptimal configuration for the processing of the modified activation site by furin in vivo.” (column 25, line 65, to column 26, line 7). Consequently, because not all proteolytic cleavage sites can be cleaved when expressed in an animal cell, the language to this effect in claim 1 clearly has patentable weight.

In claim 15, the different cell classifications represent different cell types. In this regard, the skilled artisan knows that a mammalian cell is different from a non-mammalian cell in many

respects, and that a human cell is different from a non-human cell in many respects. Consequently, because the different cell classifications represent different cell types the language to this effect in claim 15 confers patentable weight.

In claim 35, instructions can confer patentable weight when the printed matter is functional. *In re Gulack*, 703 F.2d 1381 (Fed. Cir. 1983)

Claims 1 to 4, 6 to 8, 10, 13 to 32, 34, 35 and 41 are not anticipated by WO 98/38317 (Himmelsbach), as represented by U.S. Patent No. 6,573,071. Nevertheless, solely in order to expedite prosecution and without acquiescing to the propriety of the rejection, claims 3 to 12 have been cancelled herein without prejudice and the remaining claims have been amended as set forth above. The rejection of claims 3 to 12 is therefore moot and the rejection will be addressed as if applied to the claims under consideration upon entry of the amendments.

Claim 1, and the claims depending therefrom, have been amended to recite “Factor VII or Factor IX” and a proteolytic cleavage site “having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1).” The ‘071 patent fails to teach or suggest Factor VII or Factor IX, let alone Factor VII or Factor IX and a proteolytic cleavage site “having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1).” Consequently, for these reasons alone, the ‘071 patent fails to teach each and every element of claims 1, 2, 13 to 32, 34, 35 and 41. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) over WO 98/38317 (Himmelsbach), as represented by U.S. Patent No. 6,573,071.

The rejection of claims 1, 24 and 28 under 35 U.S.C. §103(a), as allegedly unpatentable over WO 98/38317 (Himmelsbach) as represented by U.S. Patent No. 6,573,071, in view of Amalfitano et al. (U.S. Patent No. 6,328,958) is respectfully traversed. The grounds for rejection are set forth in the Office Action, page 8.

Claims 1, 24 and 28, as originally filed, would not have been obvious in view of the ‘071 patent alone, or in combination with Amalfitano et al. at the time of the invention. Nevertheless, solely in order to expedite prosecution and without acquiescing to the propriety of the rejection, claim 1 has been amended as set forth above. The rejection will be addressed as if applied to claims 1, 24 and 28, upon entry of the amendments.

Amended claim 1, and depending claims 24 and 28, recite, *inter alia*, Factor VII or Factor IX and a proteolytic cleavage site having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1). As discussed above, the '071 patent fails to teach or suggest Factor VII or Factor IX, let alone Factor VII or Factor IX and a proteolytic cleavage site having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1).

Amalfitano et al. fail to correct the deficiencies of the '071 patent. In particular, among other things, Amalfitano et al. fail to teach or suggest Factor VII or Factor IX, or Factor VII or Factor IX and a proteolytic cleavage site having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1).

Consequently, as neither the '071 patent nor Amalfitano et al. teach or suggest each and every element of amended claims 1, 24 and 28, the claims would not have been obvious in view of the '071 patent alone, or in combination with Amalfitano et al. at the time of the invention. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over WO 98/38317 (Himmelsbach), as represented by U.S. Patent No. 6,573,071, in view of Amalfitano et al. (U.S. Patent No. 6,328,958).

The rejection of claims 1, 3, 4, 13, 14 and 18 to 20 under 35 U.S.C. §103(a), as allegedly unpatentable over WO 98/38317 (Himmelsbach) as represented by U.S. Patent No. 6,573,071, in view of Berkner et al. (U.S. Patent No. 5,288,629) is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 9-10.

In order to establish obviousness under 35 U.S.C. §103(a), there must have been a suggestion or motivation to modify the reference; a reasonable expectation of success of producing the claimed invention; and the reference must teach or suggest each and every claim limitation. Both the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success *must both be found in the prior art, not in Applicants' disclosure*. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988), *Emphasis added*. “The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.” *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984); *See, also, In re Mills*, 916 F.2d 680 (Fed. Cir. 1990)

Claims 1, 3, 4, 13, 14 and 18 to 20, as originally filed, would not have been obvious in view of the '071 patent alone, or in combination with Berkner et al. at the time of the invention. Nevertheless, solely in order to expedite prosecution and without acquiescing to the propriety of the rejection, claims 3 and 4 have been cancelled herein without prejudice and claim 1 has been amended as set forth above. The rejection of claims 3 and 4 is therefore moot and will be addressed as if applied to claims 1, 13, 14 and 18 to 20 upon entry of the amendments.

Here, there would not have been any motivation to combine the '071 patent with Berkner et al. at the time of the invention. In this regard, contrary to the statement in the Office Action that "one of skill in the art would have been motivated to combine the teaching to increase the stability of Factor VII in a cell," there is no teaching or suggestion by Himmelspach or any evidence whatsoever in the '071 patent that introducing a modified cleavage site would increase stability of Factor X in a cell, let alone Factor VII or Factor IX. In this regard, even if for the sake of argument there were such a teaching or suggestion in the '071 patent, it is unclear what increased intercellular stability would accomplish since Factor X, Factor VII and Factor IX are components of the clotting cascade and therefore, function extracellularly.

As set forth in the '071 patent, a modified cleavage site is introduced into Factor X to improve the shelf life of recombinant Factor X polypeptide used to treat hemophiliacs, and to have the final product free of proteases and proteolytic intermediates which can function as active serine protease antagonists (see, column 3, lines 53-61; column 4, lines 11-26). As stated in the '071 patent, "the aim of the present invention is to provide a preparation containing a polypeptide having Factor X/Xa activity which exhibits high stability and can be activated to Factor Xa without using any of the conventional proteases, particularly those of animal origin, such as, for instance, RVV or trypsin." (column 4, lines 29-34). Thus, as the '071 patent fails to teach or suggest increasing stability of any blood clotting factor in a cell, the '071 patent fails to provide the requisite motivation to combine the teachings of Berkner et al. with the '071 patent. In view of the absence of a motivation to combine Berkner et al. with the '071 patent at the time of the invention, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

Furthermore, there must have been a reasonable expectation of success at the time of the invention. Here, as discussed above introduction of a furin cleavage site into FX and expression of this FX analogue in CHO cells did not result in protein bands corresponding to activated forms of the protein (35 kD and 31 kD) (column 25, line 65, to column 26, line 7). Even in cells

expressing endogenous furin, Himmelsbach states that rFactor X was processed "only to a very limited extent." (column 21, lines 7-12) Consequently, because the '071 patent teaches that introduction of a furin cleavage site into Factor X did not result in proteolytic cleavage when expressed in the CHO cells, or resulted in only very limited cleavage, clearly the '071 patent fails to provide a reasonable expectation of success that introducing a proteolytic cleavage site having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1) into Factor VII or Factor IX would produce a Factor VII or Factor IX that is cleaved at this cleavage site when expressed in an animal cell. In view of the absence of a reasonable expectation of success at the time of the invention, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

In sum, in view of the absence of the requisite motivation to combine Berkner et al. with the '071 patent at the time of the invention, and the absence of a reasonable expectation of success of producing Factor VII or Factor IX with a modified proteolytic cleavage site having the sequence Arg Lys Arg Arg-Lys-Arg (SEQ ID NO:1) that is cleaved at this cleavage site when expressed in an animal cell at the time of the invention, claims 1, 13, 14 and 18 to 20 would not have been obvious under 35 U.S.C. §103(a). Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over WO 98/38317 (Himmelsbach), as represented by U.S. Patent No. 6,573,071, in view of Berkner et al. (U.S. Patent No. 5,288,629).

CONCLUSION

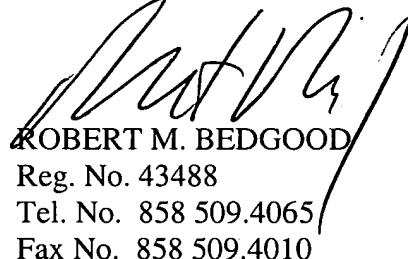
In summary, for the reasons set forth herein, Applicants maintain that claims 1, 2, 13 to 35 and 41 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

A fee of \$510 for a three-month extension of time (small entity) is incurred for filing this Response for the above-identified application. Please charge any fees associated with the submission of this paper to Deposit Account Number 03-3975, Order No. 018743-0278737. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

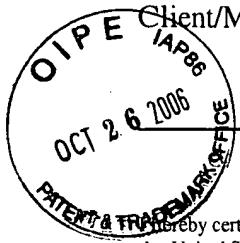
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CERTIFICATION UNDER 37 C.F.R. §§ 1.8 and/or 1.10*

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* Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(f). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.